

Replace the paragraph beginning at page 2, line 24, with the following rewritten paragraph:

a2 --Though the sites on receptors binding with these cytoplasmic tyrosine kinases (JAK kinases) are conserved among family members, the homology is not very high (Murakami et al., Proc. Natl. Acad. Sci. USA, 88:11349-11353, 1991). Actually, the sequence that best characterizes these hemopoietin receptors exists in the extracellular region. In particular, a five amino acid motif, Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:22), (wherein "Xaa" is an arbitrary amino acid), is conserved in almost all of the hemopoietin receptors. Therefore, novel receptors may be obtained by searching for novel family members using this sequence. In fact, these approaches have already led to the identification of the IL-11 receptor (Robb et al., J. Biol. Chem., 271:13754-13761, 1996), the leptin receptor (Gainsford et al., Proc. Natl. Acad. Sci. USA, 93:14564-8, 1996), and the IL-13 receptor (Hilton et al., Proc. Natl. Acad. Sci. USA, 93:497-501, 1996).--

Replace the paragraph beginning at page 3, line 10, with the following rewritten paragraph:

a3 --Initially, the inventors attempted to find a novel receptor using oligonucleotides encoding the Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:22) motif (WS motif), as the probe by plaque hybridization, RT-PCR method, and so on. However, it was extremely difficult to strictly select only those to which all 15 nucleotides that encode the motif would completely hybridize under the usual hybridization conditions, because the oligonucleotide tggag(t/c)nnntggag(t/c) (SEQ ID NO:21), (wherein "n" is an arbitrary nucleotide) encoding the motif was short, having just 15 nucleotides, and had a high g/c content. Additionally, similar sequences are contained within cDNA encoding proteins other than hemopoietin receptors, starting with various collagens that are thought to be widely distributed and also have high expression amounts, which makes the screening by the above-mentioned plaque hybridization and RT-PCR extremely inefficient.--

Replace the paragraph beginning at page 4, line 15, with the following rewritten paragraph:

Q4 --The above nucleotide sequence was used to design specific oligonucleotide primers. The primers were used to perform 5'- and 3'-RACE using cDNA libraries from human fetal hepatocytes and human placenta as the template. As a result, a full-length cDNA, NR10.1, encoding a transmembrane receptor of 652 amino acids was isolated, and the whole nucleotide sequence was determined. At the same time, a cDNA clone, NR10.2, presumed to be a splice variant of NR10, was also successfully isolated from the 3'-RACE product. Based on the determined nucleotide sequence, NR10.2 was suggested to encode a soluble receptor-like protein of 252 amino acids. It was revealed that the cysteine residues, proline-rich motif, and WSXWS (SEQ ID NO:22) motif, in the extracellular domain that is conserved among the receptor family members, the box1 motif in the intracellular domain that is implicated in signal transduction, and so on were well conserved in the primary structure of NR10.1. Therefore, NR10.1 was considered to encode a typical hemopoietin receptor.--

Replace the paragraph beginning at page 36, line 9, with the following rewritten paragraph:

Q5 --FIG. 1 shows the nucleotide sequence of AQ022781 (SEQ ID NO:34) identified in the gss database. The deduced amino acid sequence (SEQ ID NO:35) is shown under the predicted exon sequence. The YR motif and WS motif that were used as the target are boxed. Two "n" in the nucleotide sequence are also boxed.--

Replace the paragraph beginning at page 36, line 13, with the following rewritten paragraph:

Q6 --FIG. 2 shows partial amino acid sequences of NR10 (amino acid residues 198-238, 201-237, 196-237, 189-238, and 196-239 of SEQ ID NO:4, respectively) found in the sequence of AQ022781 (SEQ ID NO:35, which is part of SEQ ID NO:4), and those of known hemopoietin receptors having homology thereto. Identical residues are boxed with shadow, and similar residues are shadowed. Gap spaces are underlined. Known hemopoietin receptors are, from top,

Q6 human gp130 (GenBank Accession No. NM002184.1; IL6ST; SEQ ID NO:36), human LIF receptor (GenBank Accession No. NM002310.1; LIFR; SEQ ID NO:37), human Oncostatin M receptor β subunit (GenBank Accession No. NM003999.1; OSMR; SEQ ID NO:38), human IL-12 receptor β 2 subunit (GenBank Accession No. NM001559.1; IL12RB2; SEQ ID NO:39), and human NR6 (GenBank Accession No. AC003112; SEQ ID NO:40).--

Replace the paragraph beginning at page 36, line 21, with the following rewritten paragraph:

Q7 --FIG. 3 shows the nucleotide sequence of the full length NR10.1 cDNA (SEQ ID NO:1) that was obtained by combining the 5'- and 3'-RACE products. The deduced amino acid sequence encoded by NR10.1 is also shown (SEQ ID NO:2). The amino acid sequence predicted to be the secretion signal sequence is underlined. The predicted transmembrane domain is shadowed. Conserved cysteine residues and the WS motif are boxed.--

Replace the paragraph beginning at page 36, line 28, with the following rewritten paragraph:

Q8 --FIG. 6 shows the nucleotide sequence of the full length NR10.2 cDNA (SEQ ID NO:3) that was obtained by combining the 5'- and 3'-RACE products. The deduced amino acid sequence encoded by NR10.2 is also shown (SEQ ID NO:4). The predicted secretion signal sequence is underlined. Conserved cysteine residues and the WS motif are boxed.--

Replace the paragraph beginning at page 37, line 14, with the following rewritten paragraph:

Q9 --FIG. 13 shows the nucleotide sequence of the full length NR10.3 cDNA (SEQ ID NO:16). The deduced amino acid sequence encoded by NR 10.3 is also shown (SEQ ID NO:17). The predicted secretion signal sequence is underlined. The amino acid sequence predicted to be the transmembrane domain is colored. Conserved cysteine residues and the WS motif are boxed.--

Replace the paragraph beginning at page 37, line 25, with the following rewritten paragraph:

Q10 --The inventors aimed at finding another motif conserved among the hemopoietin receptor family, in addition to the Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:22) motif (WS motif), in order to design an oligonucleotide probe including both motifs together. The inventors examined the sequence of other regions for another motif. As a result, they found a tyrosine or histidine residue in the extracellular domain of the family proteins, located 13 to 27 amino acids upstream of the WS motif, that is conserved at high frequency. They further examined the six amino acid residues located to the C-terminus from the Tyr/His residue for a consensus sequence that appears with a high-frequency, and found the amino acid following sequence: (Tyr/His)-Xaa-(Hydrophobic/Ala)-(Gln/Arg)-Hydrophobic-Arg (referred to as the YR motif in the following). However, the YR motif is not considered as a perfect consensus sequence, and also the combination of nucleotide sequences that can encode the motif is really complicated. Thus, it seemed very difficult to synthesize all the nucleotide sequences that encode the amino acid sequence and provide them as the probe for hybridization, a practical method of screening, or as the primer for RT-PCR.--

Replace the table beginning at page 38, line 24, with the following rewritten table:

--Table 1

Q11

YR motif	spacer amino acids	WS motif
YTVQVR	AR XXXXXX GT	WSEWSP
(SEQ ID NO:23)	(SEQ ID NO:26)	(SEQ ID NO:29)
YEARVR	VQ XXXXXX GY	WSDWSE
(SEQ ID NO:24)	(SEQ ID NO:27)	(SEQ ID NO:30)
YSLQLR	CK XXXXXX GI	WSPWSQ
(SEQ ID NO:25)	(SEQ ID NO:28)	(SEQ ID NO:31)--

Replace the paragraph beginning at page 40, line 25, with the following rewritten paragraph:

Q12 --AQ022781 (SEQ ID NO:34) is the terminal sequence of a BAC clone consisting of 459 bp, deposited in the gss database. It was the only clone that was also positive in both searches using partial amino acid sequences of human gp130 or LIF receptor as the query respectively. It was presumed that the reliability of the sequence might be low due the existence of two "n" in the middle and the nature of the deposition system of the Genomic Survey Sequence. Nevertheless, as shown in Figure 1, a splice consensus sequence could be recognized as the "ag" sequence following the "c/t" rich sequence at 175th to the 218th bases, and it was predictable that it contains an exon starting from "atg" following the splice consensus sequence. Then, the predicted exon sequence was used to search on the nr database in GenBank using BlastX (Advanced BlastX 2.0.8). The results revealed that the exon has homology to many known hemopoietin receptor genes as shown in FIG. 2. The result was: (1) AQ022781 (SEQ ID NO:35) contains a YR motif, sequence [YVIALR] (SEQ ID NO:32), and that it retained a complete WS motif, sequence [WSDWS] (SEQ ID NO:33); (2) showing homology with several known hemopoietin receptors, and (3) both of the two Ser residues in the WS motif are encoded by AG(C/T). And thus, it was predicted that the gene could encode a novel hemopoietin receptor gene. The codon for Ser in the WS motif is generally AG(C/T) in most of the known hemopoietin receptors, but the second Ser residue in the EPO receptor, TPO receptor, and mouse IL-6 receptor is encoded by TCN. Indeed, most of the false positive clones containing by chance a WS motif-like sequence, the second Ser was mostly encoded by TCN. Thus, the Ser residue encoded by the AG(C/T) codon could be used as a marker for selection of positive clones. Accordingly, specific oligonucleotide primers were designed from the predicted exon sequence on AQ022781, and used for 5'-RACE and 3'-RACE method as below.--

Replace the paragraph beginning at page 46, line 6, with the following rewritten paragraph:

Q13 --First, it is predicted that the sequence from the 1st Met to the 32nd Ala in the common extracellular domain of NR10.1 and NR10.2 is the typical secretion signal sequence. Herein, the 1st Met is presumed to be the translation initiation site because there exists an in frame termination codon at the (-2) position. Next, a typical ligand-binding domain exists in the region from the 43rd Cys to the 53rd Cys or the 55th Trp residue. In addition, the 81st and 94th Cys correspond to the Cys residue repeat conformation well conserved among other hemopoietin receptor family. Furthermore, a Pro-rich region (PP-W motif) beginning at the consecutive Pro residues at positions 137 and 138 to the 157th Trp residue is conserved, and residues from the 210th Tyr to 215th Arg corresponds to the YR motif above. A typical WSXWS-box (WS motif; SEQ ID NO:22) is also found at residues from the 224th Trp to 228th Ser.--

Replace the paragraph beginning at page 46, line 17, with the following rewritten paragraph:

Q14 --The open reading frame (ORF) of NR10.2 encodes 24 amino acids from the WSXWS sequence (SEQ ID NO:22) and terminates at the stop codon thereafter. Thus, it encodes a soluble hemopoietin receptor-like protein without a transmembrane region. On the other hand, the ORF of NR10.1 contains a typical transmembrane domain of 24 amino acids from the 533rd Ile to the 556th Leu residue following the above motifs. In addition, the intracellular domain adjacent to the transmembrane domain contains Pro residues at positions 571 and 573, corresponding to the Box-1 consensus sequence (PXP motif) well conserved among other hemopoietin receptors and is considered to be implicated in signal transduction. These features above confirm that the NR10 gene encodes a novel hemopoietin receptor protein.--